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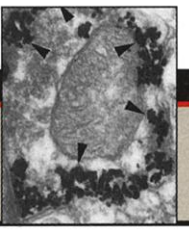
Conservation and people in Africa



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A role for natural cannabinoids

BIOCHEMISTRY

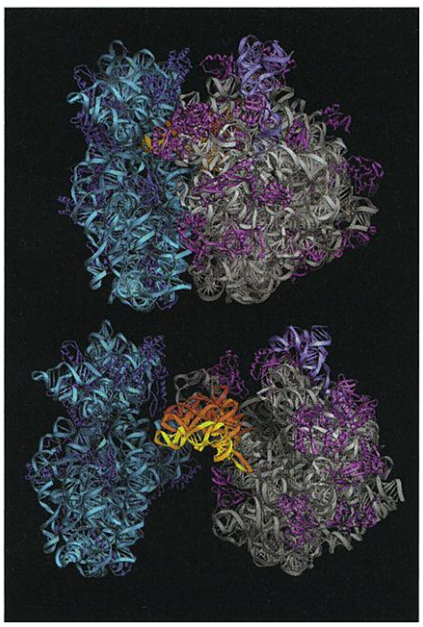
Ribosome's Inner Workings Come Into Sharper View

In the latest in a series of stunning advances, a team of structural biologists has unveiled the most comprehensive view yet of one of the cell's most critical components: the ribosome.

While DNA carries instructions for building proteins, ribosomes actually do the work. They produce proteins by stitching together amino acids carried in by transfer RNA (tRNA), according to instructions transmitted from DNA in the nucleus by messenger RNA. Biologists have long wondered just how this factory churns out the thousands of different proteins necessary for life.

Now, as reported online this week in *Science* (www.sciencexpress.org), a team led by Harry Noller at the University of California, Santa Cruz (UCSC), presents a molecular view of a complete bacterial ribosome, describing its structure down to 5.5 angstrom resolution. Although that resolution is not high enough to discern the positions of individual atoms in this giant complex of proteins and RNA—which means that more work needs to be done to verify the new analysis—it "represents a huge step forward," says Peter Moore, a Yale biochemist.

Over the past few years, Moore and others have obtained progressively more detailed structures of the two major components, called subunits, of the ribosome. Moore, with Yale's Thomas Steitz and their colleagues, recently published the highest resolution structure yet of the large subunit (*Science*, 11 August 2000, p. 905). But Noller's team is the first to provide a detailed view of the entire molecule. (The group produced a blurrier image, at roughly 7.8 angstrom resolution, in 1999.) Thanks to this new work, researchers can now see "how the two subunits are interconnected and what kind of environment they [provide] the tRNA," says Joachim Frank, a cryoelectron microscopist at the Wadsworth Center in Albany, New York. "This is exactly the kind of information that is entirely missing from the previous atomic structures."



Putting it all together. An exploded view (bottom) of the whole ribosome (top) reveals the positioning of the three tRNAs (red, orange, yellow) relative to the small (dark blue/cyan) and large (gray/magenta) subunits.

To pull off this feat, says Noller collaborator Jamie Cate, who is now at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, "we had to try out a bunch of things" without really knowing in advance what it would take to get a higher resolution image.

Cate's colleagues Marat Yusupov and Gulnara Yusupova, now at CNRS's Biology and Structural Genomics Institute in Strasbourg, France, were the chemistry gurus who worked out the conditions for building ribosome crystals good enough to analyze. One secret seemed to be adding two or three tRNAs to the crystallizing ribosome. When these tRNAs moved into their docking sites on the ribosome, they likely stabilized the structure, allowing for a sharper image, Cate suggests. An added bonus: The three-tRNA complex also captured the ribosome when protein production is in full swing—offering new insights into how proteins are made.

Those insights are sorely needed. Despite years of research, biologists still have an incomplete picture of protein production, says Cate. They know, in general, that incoming tRNAs, each bearing a specific amino acid, shuttle through a series of three docking sites along the interface of the ribosome's two subunits. As the tRNAs move across these sites, they release their cargo and make way for the addition of the next amino acid in the growing protein chain.

Last August, Moore and his colleagues demonstrated that the ribosome's RNA—not its 54 proteins, as expected—catalyzed the linking of the amino acids. The new UCSC data, refined and improved upon by the incorporation of existing structural and biochemical results, are now revealing some specifics of this shuttling, called translocation.

"First of all, we could see the distances the tRNAs have to move during translocation, which are considerable—20 to 50 angstroms," says Noller. For a molecule, that's quite a leap, he adds. Moreover, they can see that to make these moves, the tRNAs have to wriggle past quite a few obstacles, namely, contacts with the surrounding ribosome that stabilize the docked tRNA.

Because the structure clearly reveals placement of the tRNAs in the three docking sites, says Wolfgang Wintermeyer of the University of Witten/Herdecke in Germany, it also reveals the extent of contact—where the tRNA and the ribosome "touch." Until now, these contacts had only been hinted at in biochemical studies and in the Noller group's fuzzier ribosome structure.

The Noller group observed, for example, that a prominent kink in tRNA—dubbed "the elbow"—somehow reaches out to ribosomal proteins at each of the three docking sites as it moves into them. The team also saw that some ribosomal proteins have spidery "tails" that hang down into these sites and interact with the backbone of the tRNA, helping keep it in place momentarily. As a result, "we know pretty much what is binding the tRNA to the ribosome," Noller explains, because the work shows that ribosomal proteins, and not just ribosomal RNA, are involved.

As the researchers hoped, the new structure brings into clearer focus parts of the large subunit that were blurred in the structure Moore's team produced nearly 8 months ago. Analysis of the interactions of the large subunit with the small subunit indicate that the two subunits have to move to allow tRNA to traverse the ribosome during translocation, says Wintermeyer. Thus, translocation likely also involves the dissolution of the molecular bridges between the subunits.

CREDIT: M. YUSUPOV *ET AL.*

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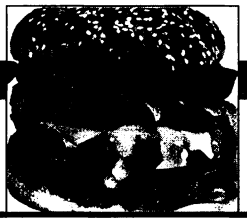
Food sources and climate change

2536
The complex puzzle of dietary fat



In all, the UCSC structure reveals about 30 of these molecular connections, quite a few more than the six first discerned by Frank's cryoelectron microscopy studies in the mid-1990s. Frank thinks that some of these bridges—the exact chemical nature of which is still unclear—help keep the two subunits in register with one another. Others—likely those in contact or close to the tRNAs—communicate the status of protein production, and the rest participate either passively or actively in the movements of the subunits themselves as they ratchet, possibly making room for tRNA movement.

Like Frank, Moore sees these bridges as key: "The making and breaking of these bridges are almost certainly part of the protein synthesis process." Therefore, a logical next step, which several teams will likely pursue, would be to make mutations that alter these bridges in specific ways to observe the effects of those changes on protein production.

But some biologists, especially Noller, Cate, and their colleagues, will not be diverted from their quest to make even better crystals to get ever closer to a view of the atoms behind the ribosome's many parts. Says Moore: "You never run out of your desire to go after ever higher resolution."

–ELIZABETH PENNISI

RESEARCH REACTORS

German Neutron Source Faces New Demands

BERN, SWITZERLAND—Plans to open a long-awaited neutron source this fall in Garching, near Munich, were thrown into confusion last week after the German cabinet called for a change in the research reactor's fuel source to avert a potential proliferation threat. It also said the State of Bavaria, rather than the federal government, should pick up the tab for building a storage facility—which might cost as much as the reactor itself—to dispose of spent fuel elements. Unless a compromise is reached, those new demands could delay the start-up of the $500 million FRM-II reactor and make its operations more expensive.

In a 21 March statement, the cabinet said the nearly completed reactor, designed to use highly enriched uranium (HEU) fuel, should shift to medium enriched uranium (MEU) fuel within 5 years. That would bring it in line with an international effort to phase out HEU-fueled research reactors, mainly because of fears that terrorists could divert HEU for nuclear bombmaking. The cabinet's negotiating position—developed with input from both the research and environment ministries—sets up delicate talks between federal officials and those in the Bavarian government, which has resisted a rapid conversion to MEU fuel and has insisted that nuclear-waste storage is a federal responsibility. Berlin, however, holds a trump card: FRM-II must receive a final permit from the environment ministry before it goes on line.

The political sensitivity of using HEU fuel is not new. In the mid-1990s, the U.S. government pushed for the Technical University of Munich, which will house the FRM-II, to redesign the reactor to use less-enriched uranium (*Science*, 4 August 1995, p. 628). Bavarian officials refused, and the dispute died down until a coalition of Social Democrats and Greens took power late in 1998 and appointed an expert committee to examine the fuel question. In June 1999, the panel suggested that conversion would be a good thing, but that it would be costly and time consuming to alter the FRM-II's design. Some experts favored postponing conversion—which would cost as much as $55 million—until a new generation of high-density MEU fuel (based on a uranium-molybdenum alloy now used in some Russian reactors) is developed, probably by 2008 (*Science*, 25 June 1999, p. 2065). Bavaria's science minister, Hans Zehetmair, started talks this week with federal research minister Edelgard Bulmahn. Zehetmair told *Science* that the cabinet's proposed deadline for the reactor's conversion to MEU—1 January 2006—is untenable. "You can't yet set an exact date because scientists are still trying to improve the MEU fuel," he says. And Bavaria opposes building a separate nuclear-waste storage facility for the FRM-II, Zehetmair says, because "the law makes it clear that this is a federal responsibility."

Caught in the middle of the dispute are scores of physicists, materials scientists, and structural biologists who have labored for years on instruments for the FRM-II's beam lines. "They need a clear message about its future," says Winfried Petry, a Technical University physicist who heads the FRM-II's scientific board. "Some of these instruments are unique, and others are the best of their kind worldwide."

The two dozen instruments for the beam lines (see chart) include the Munich Accelerator for Fission Fragments (MAFF), a machine designed by University of Munich physicist Dieter Habs that would smash neutron-rich nuclei into heavy elements to forge long-lived superheavy elements with atomic numbers up to 126. "We'll be extremely disappointed if [a political contretemps] causes a delay" in the FRM-II start-up, Habs says. And the longer the reactor is in limbo, the more

A SAMPLING OF FRM-II INSTRUMENTATION

- RESEDA neutron resonance "spin echo" spectrometer
- High-resolution "time-of-flight" spectrometer with cold neutrons
- Crystal time-of-flight spectrometer
- Small-angle scattering diffractometer
- REFSANS diffractometer for reflectometry and small-angle scattering
- Instruments for long-wavelength neutrons
- BSM back-scattering spectrometer
- PANDA three-axis spectrometer for cold neutrons
- PUMA double-focusing three-axis spectrometer with thermal neutrons
- Ultracold neutron source
- Instrument for fundamental physics with cold neutrons
- Radiography/tomography with cold neutrons
- MAFF fission fragment accelerator
- HEIDI single-crystal diffractometer with hot neutrons

Hot debate. A proposed fuel change could delay start-up of the FRM-II reactor.

SOURCE AND CREDIT: FRM-II, GARCHING